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Diagnostic and prognostic problems with the Prader-Willi syndrome

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ABSTRACT

Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder resulting from chromosomal duplications, deletions, or imprinting within the 15q11-q13 region. In most cases, patients with PWS inherit a de novo paternally inherited deletion, and the remaining result from maternal disomy 15 and imprinting. Currently, DNA methylation analysis remains the gold standard for diagnosing PWS. However, this diagnostic test provides no information concerning the molecular class of PWS. As a result, clinicians remain unable to accurately determine diagnostic and prognostic information for patients with PWS. Further research is needed toward establishing standardized, accurate, and cost-effective testing methods for diagnosis and treatment of patients with PWS.

KEYWORDS Chromosomal deletion; chromosomal duplication; imprinting; Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder resulting from chromosomal duplications, deletions, or imprinting within the 15q11-q13 region.[1] These patients typically present with obesity, hypotonia, mental retardation, short stature, and hypogonadotropic hypogonadism, suggesting an underlying hypothalamic dysfunction.[2] In most cases, patients with PWS inherit a de novo paternally inherited deletion; the remaining cases result from maternal disomy 15 and imprinting.[3]

Despite the uniqueness of PWS, overlap with other clinical conditions requires DNA testing for a definitive diagnosis.[4,5] According to the American Academy of Pediatrics, "Diagnostic testing for PWS should begin with methylation analysis to confirm the absence of paternally imprinted genes in the PWS region of chromosome 15. When only a maternal methylation pattern is seen … additional testing is needed to identify the specific cause, which allows for appropriate counseling regarding recurrence risk."[6] However, this diagnostic test provides no information concerning the molecular class of PWS, including paternal deletion, maternal disomy, or imprinting defects.[7] As a result, clinicians remain unable to accurately provide patients with PWS and their families effective treatment, diagnostic, and prognostic information.[1,8] For example, different molecular classes alter the severity of behavioral issues of adult patients with PWS and its occurrence in succeeding generations.[9,10] The problem is further complicated by the increasing number of novel mutations associated with PWS and atypical presentations.[11,12] Furthermore, the exact genetic contribution associated with the clinical features of PWS remains uncertain.[13] Consequently, the gap between clinical diagnosis and identifying the molecular mechanisms behind PWS increases with each novel mutation discovered.

Despite genetic advances in diagnosing PWS, several limitations remain within clinical genetics preventing clinicians from fully informing patients with PWS of their diagnostic and prognostic information. Current guidelines do not require genetic laboratories to maintain a universal standard for genetic tests or for screening genetic variants associated with PWS.[14] Genetic laboratories also face several limitations in separating patients with PWS from the high volume of genetic referrals, enabling patients easy access to genetic testing, and controlling the costs of genetic tests.[14–16] As such, clinicians need more guidance in accessing and understanding the various clinical scenarios involved in PWS genetic testing.[14]

In response to these clinical dilemmas, current guidelines encourage physicians to order additional genetic testing for any patient suspected of having or diagnosed with PWS.[1,14]

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However, additional testing increases the cost of genetic analysis and the technical expertise required to analyze and interpret the results.[14] Specifically, "the cost of these various tests varies from one laboratory or genetic service to another. Some will charge for a complete diagnosis, others charge for each step of the process (e.g., DNA extraction, a cytogenetic harvest, slide making, cytogenetic analysis) so that a useful comparison cannot be made. The less tests required, the more cost effective the diagnosis becomes."[14] Furthermore, the lack of effective treatments targeting specific molecular classes of PWS increases the cost and difficulties faced by PWS patients. As a result, "that PWS-related costs are so drastically and disproportionately high compared with individuals without PWS, however, speaks to the need for effective treatments to improve patient survival and quality of life and to reduce the financial burden on patients and families."[17] More discussion and research are needed to establish standardized, accurate, and cost-effective testing methods for diagnosing and treating patients with PWS. Clinicians should remember that the certainties expected from genetic testing may be elusive.

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